

REMARKS

Claims 99-103 have been amended to address indefiniteness. Support for the amendments is found in the existing claims and the specification. Accordingly, the amendments do not constitute the addition of new matter. Arguments and a Declaration under 37 C.F.R. § 1.132 are presented to rebut the rejection of the claims as obvious. The Examiner's withdrawal of the rejection of the claims as anticipated and acceptance of the Replacement Drawings is gratefully acknowledged.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 99-107 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims have been amended to correct antecedent basis. In view of the amendments, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 99-107 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Selvais, et al. (J. Cardiac Failure 6: 201, 2000), Hülsmann, et al. (J. Am. Coll. Cardiol. 32: 1695, 1998), Rousseau, et al. (Circulation 108 (17 Suppl.): IV-556, 2003), Berger, et al. (J. Heart Lung Transplant. 22: 1037, 2003), and Sabatine, et al. (Circulation 105: 1760, 2002).

The present claims are directed to the use of two markers: 1) Big ET-I (1-38) and 2) either N-proANP (1-98) or N-proANP (68-98) to determine the likelihood of death from a cardiovascular cause and to categorize these individuals into groups having a high, intermediate or low survival prognosis.

The prior art cited by the Examiner in the Office Action is summarized below with regards to disclosure of the markers claimed by Applicants.

Selvais, et al. (2000) teach that ET-I (i.e., a smaller fragment than Big ET-1) and N-proANP are associated with death in patients with congestive heart failure (CHF). Selvais, et al. teach use of the two markers together to stratify patients into low, medium and high risk (Figure

1). However Selvais, et al. (2000) do not teach anything regarding predictive effects of Big ET-1. In fact, Selvais, et al. state that “No direct comparison of the prognostic value of ET-1 and big ET has been achieved to date” (page 205, col. 1, first paragraph). Based upon the disclosure of Selvais, et al., there is no reasonable predictability of success that Big ET-1 could be substituted for ET-1.

Hüllsmann, et al. teach the predictive value of Big ET-1, but do not teach the use of two markers together and do not teach prediction of long term survival.

Rousseau, et al. confirm that both ET-1 and Big ET-1 are strong independent predictors of patient survival for CHF. However, Rousseau, et al. do not teach use of two markers together.

Berger, et al. also teach that Big ET-1 is a good predictor for patients with severe CHF, but that N-proANP is a better marker for patients with mild or moderate CHF. Berger, et al. teach both markers, but not used together.

Sabatine, et al. does not teach either Big ET-1 or N-proANP. However, Sabatine, et al. teach the use of multiple markers to predict outcome for patients with acute coronary syndromes.

Accordingly, while none of the references teach the use of Big ET-1 and N-proANP together to predict low, medium and high risk of mortality from CHF, taken together, the references teach the elements of the invention thus establishing a *prima facie* case of obviousness. Based upon the references cited above, one of ordinary skill in the art would reasonably expect to substitute ET-1 of Selvais, et al. with Big ET-1 and expect to have similar results.

However, Applicants have found that ET-1 and Big ET-1 are not equivalent and that the combination of markers Big ET-1 and N-proANP allows for prediction of patient outcome, particularly in medium and mild cases of CHF, which was not known prior to invention by Applicant and not predictable from the combination of references discussed above.

As stated in M.P.E.P. 716.02(a), ““A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue.” *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985).” and “Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness.” (citing *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)).

Such unexpected results are shown in the attached Declaration. The Declaration shows that, contrary to expectations from the prior art cited above, ET-1 and Big-ET-1 are not interchangeable and also that the combination of Big ET-1 and N-proANP allows prediction of patient outcome that was unexpected in view of the references cited above.

ET-1 and Big-ET-1 are not interchangeable

As shown by comparison of Figures 1 and 2 in the Declaration, Big-ET-1 is a better predictor of survival than ET-1, particularly over a longer period - times over 60 months. This would not have been expected from the prior art cited above, particularly Berger, et al., who teach the Big-ET-1 is preferred for short term survival prediction and that N-proANP is better at predicting long term survival. Such differences are even more marked when the patient population has mild CHF as shown in Figures 3 and 4. ET-1 has almost no predictive value for these patients.

The combination of Big ET-1 and N-proANP allows prediction of outcome for patients with severe, moderate and mild CHF

As discussed in the Declaration, the results shown by Selvais, et al. are misleading because 1) the assay used by Selvais, et al. was not specific to ET-1 and 2) Selvais, et al. did not separate severe and mild CHF patients. By the side-by-side comparison shown in the Declaration, the unexpected advantage in combining Big-ET-1 with N-proNP is shown that could not have been predicted from the prior art.

In view of Applicants' arguments and the attached Declaration, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this

application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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